



Faculty of Pharmacy

Anthraquinones

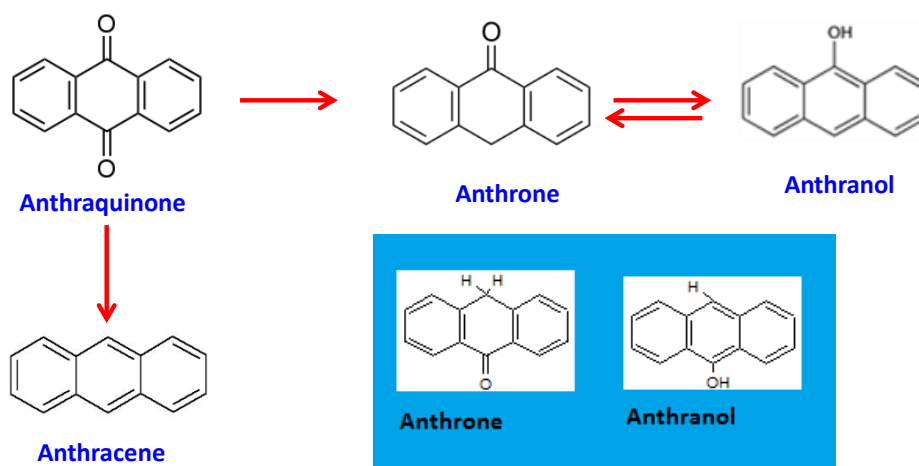
Pharmacognosy and Phytochemistry



Dr. Yousef Abusamra

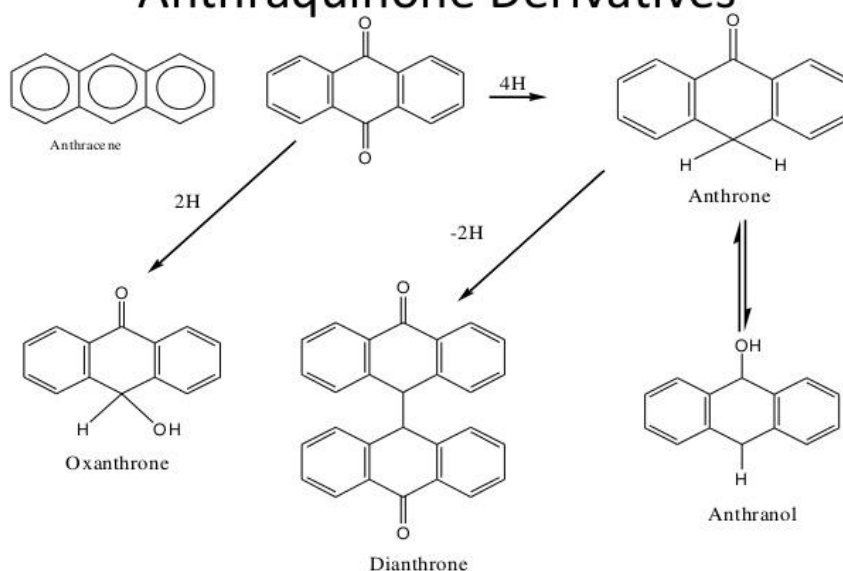
Anthraquinone Glycosides

- The anthraquinone moieties are 5 general groups and these are derived from:

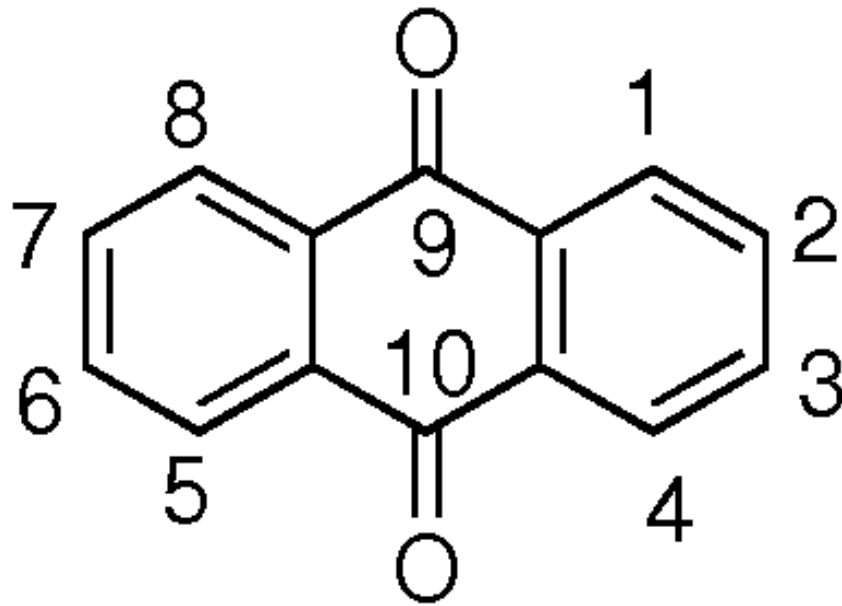


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Anthraquinone Derivatives



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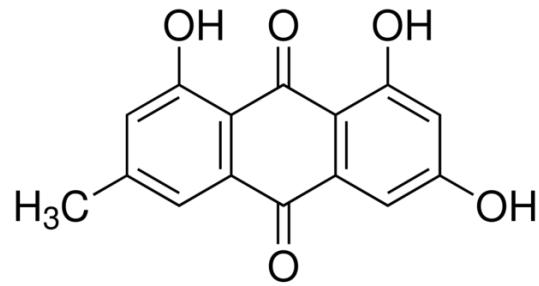


3

- The free anthraquinone aglycones exhibit little therapeutic activity.
- The sugar residue facilitates absorption and translocation of the aglycone to the site of action.
- The anthraquinone and related glycosides are stimulant cathartic and exert their action by **increasing the tone of the smooth muscle in the wall of large intestine**.
- A research on rhein glycosides shows that this compound increases pressure on the walls of the colon **{They are irritant and stimulate peristaltic movement}**, thus pushing the stools outside.
- We have 4 general types of anthraquinone glycosides according to the differences in the chemical structure, and these are:

4

1. Emodin:

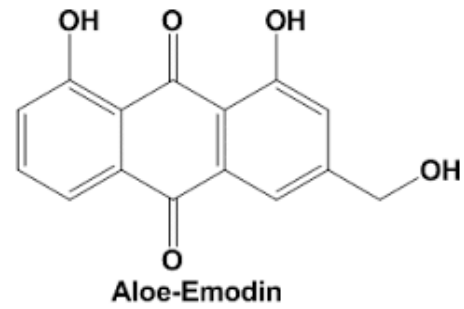


1, 3,8-trihydroxy-6-methyl anthraquinone

2. Aloe-emodin:

❖ 1,8-dihydroxy-3-(hydroxymethyl)-9,10-anthraquinone

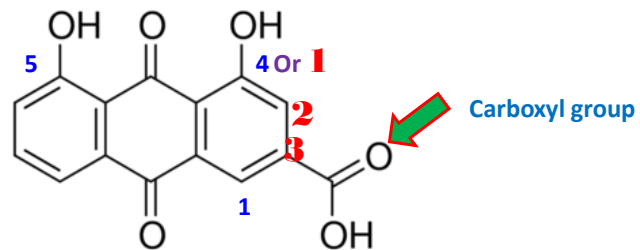
❖ 1,8-dihydroxy-3-(hydroxymethyl)anthracene-9,10-dione.



Aloe-Emodin

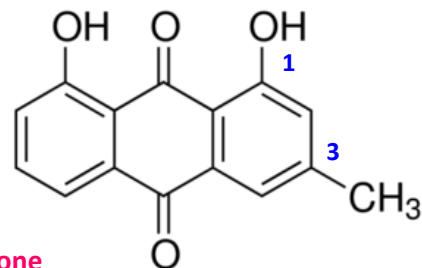
5

3. Rhein:



4, 5-dihydroxy -9,10-dioxoanthracene-2-carboxylic acid

4. Chrysophanol:

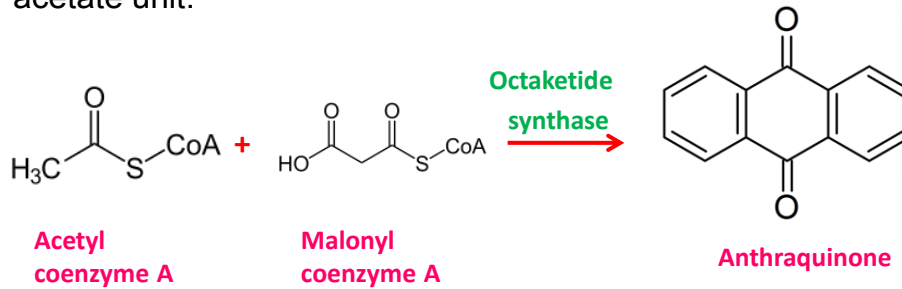


1, 8-dihydroxy -3-methyl anthraquinone

6

Biosynthesis:

- The biosynthesis of all secondary metabolites have revealed the existence of 3 very important biosynthetic routes: the **acetate**, **mevalonate** and **shikimic acid** pathway.
- **Most** anthraquinone glycosides aglycones are derived from the **acetate pathway**, which usually starts from **acetic acid** units which will form the active form **acetyl Co enzyme A**, which will then form the **malonyl Co enzyme A** by the addition of another acetate unit.



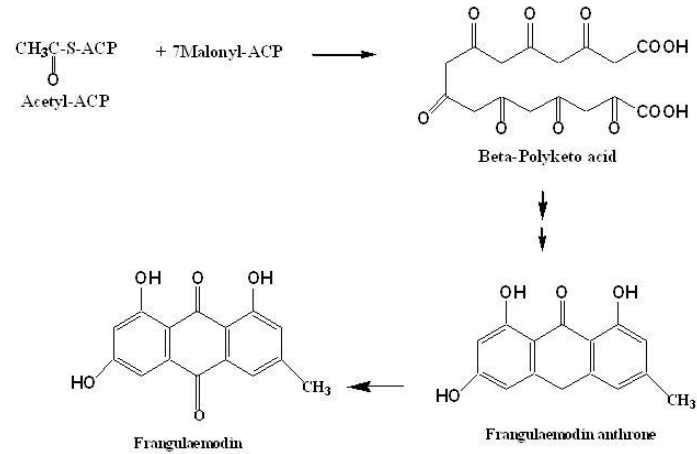
7

Biosynthesis of Anthraquinones

- Mainly produced via acylpolymalonate (acetate-malonate) pathway in Polygonaceae & Rhamnaceae & Leguminosae....
- Starts with acetyl CoA carboxylation to malonyl CoA then continues in the usual way of formation of the poly-keto-methylene-chain with simultaneous loss of CO₂ followed by cyclisation
- Shikimate-mediated in Rutaceae, Rubiaceae & Gesneriaceae
مثال نبات المديدة، غزنرية فوية، تشمل العديد من الرتب مثال القهوة

15

In the biosynthesis of the **anthraquinones** for the formation of the poly-keto-methylene-chain : **1 acetyl CoA and 7 Malonyl CoA** are used.



9

• DRUGS CONTAINING ANTHRAQUINONES:

1. *Cascara sagrada*: القشيرة المقدسة

➤ Is the dried bark of *Cascara purshiana* النبق، السدر، [Rhamnaceae النبقيات، السدریات].

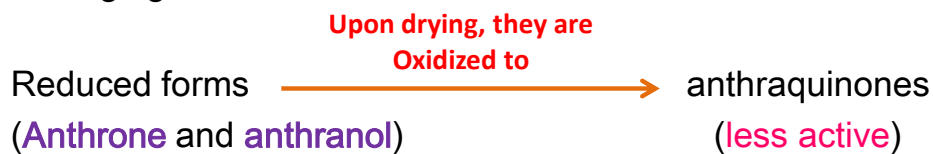


Native to western North America

The Bark

19

- It should be aged for at least one year prior to use in medicinal preparations as a cathartic.
- **Reduced** forms of emodin-type glycosides predominate in **fresh bark** which is **oxidized** to the anthraquinones after this one year of aging.

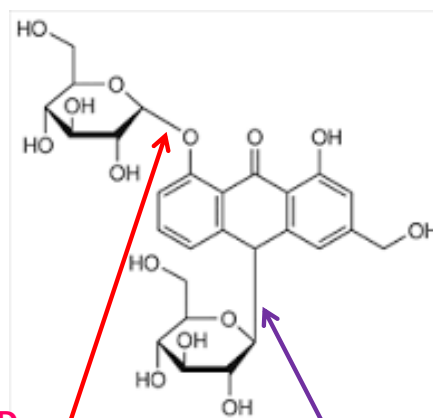


Constituents:

- Two types of anthracene compounds (6-9%) and these consist of:
 - a) C-glycosides 80-90%
 - b) O-glycosides 10-20%.
 - c) mixture of both.

11

- O-glycosides: the principle O-glycosides are of **aloe-emodin** type which are **cascarosides A, B, C, D**.



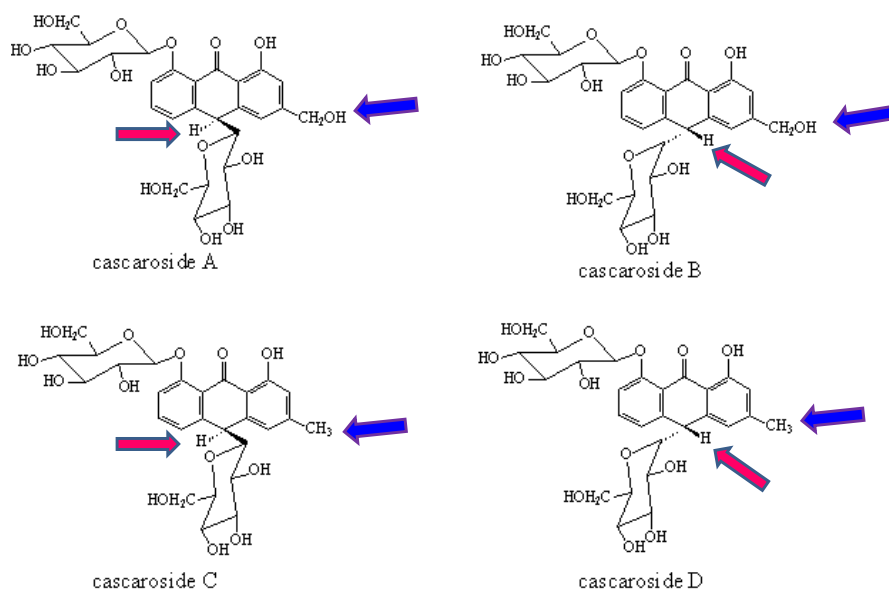
Cascaroside A, B, C, and D

All Include:

• O-glycosides.

• C-glycosides.

12



➤ **Uses, indication and action:** laxative (adj.) = purgative (adj.) = a cathartic (noun).

13

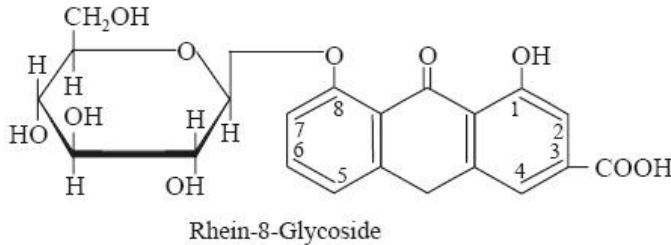
2. Rhubarb: الرواند

➤ Is the **rhizome** of *Rheum palmatum* L and *Rheum officinale*. (F. Polygonaceae الرواندية).



14

- The main constituent is **rhein** which is **rhein- 8-glucoside**.



Also, contains **TANNINS**
That are constipative,
therefore
rhubarb is a **MILD LAXATIVE**

- **Uses, indications and action:** laxative (adj.) = purgative (adj.) = a cathartic (noun).

3. Aloe: الصببر

- **Dried juice** obtained by evaporation of the liquid drained from the transversely cut leaves of various species of aloe.
 - Aloe barbadensis (vera)*: (F. Liliaceae): which will form Curacao aloe (common name).
 - Aloe ferox*: Cape aloe (common name).
 - Aloe perryi*: Zanzibar variety (common name).

15



Aloe vera (barbadensis)



Aloe ferox



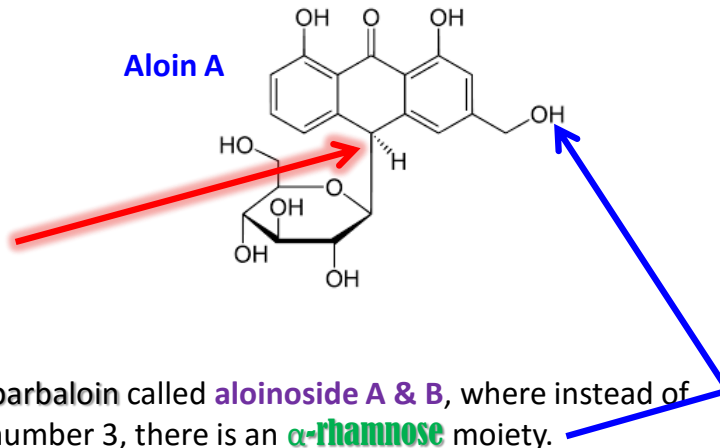
Aloe perryi

16

• **Constituents:**

- a) The main constituent is **barbaloin** which is a **C-glycoside**.
 ➤ It is a mixture of **aloin A** (10-**R**-isomer) and **aloin B** (10-**S**-isomer).

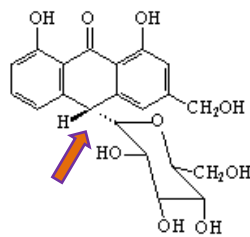
Alain A differs from alain B just by the orientation of the substituents on C-10



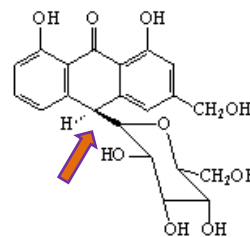
- b) **O-glycoside** of barbaloin called **aloinoside A & B**, where instead of the **H-atom** at number 3, there is an **α -rhamnose** moiety.

❖ **Alainoside A differs from alainoside B just by the orientation at C-10.**

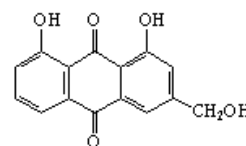
17



aloin B



aloin A



aloe-emodin

18

- **Uses:**

1. Laxative.
2. The juice which is a complex structure contains polysacharrides used for wound healing and burns , (for skin as gel).



19

4. Senna:

- Dried leaflets of:
 - a) *Cassia acutifolia*: (Alexandrian senna)
 - b) *Cassia angustifolia*: (Indian senna or Tinnevelly senna)
- Both belong to the family **Leguminosae** or **Fabaceae**.

Alexandrian senna

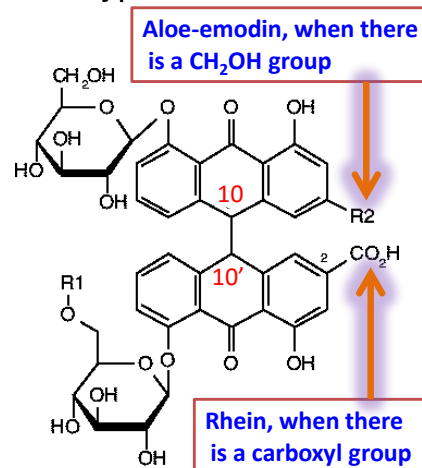


20

- **Constituents:**

- The main constituents are **O-glycosides sennosides** which are an example of dianthrones and these are dimeric glycosides.
- The aglycones are **aloe-emodin** and **rhein** type and these are:

- **R2** **10-10'**
- Sennoside A COOH trans
- Sennoside B COOH cis
- Sennoside C CH₂OH trans
- Sennoside D CH₂OH cis



- This implies that sennoside A and B, which are the main components, are **dianthrones** and have their aglycones as **rhein** but **stereoisomers** (i.e. **trans** and **cis** at the connection bridge **10-10'**).

21

- Sennoside C and D are **heterodianthrones**, i.e. the aglycones are **rhein** and **aloe-emodin**.
- **Uses and action:** laxative and cathartic at dose of **2g**.



22

5- Frangula: السدر أو النبق أو السويد

- The dried bark of *Rhamnus frangula* or *Rhamnus purshiana* (Fam. *Rhamnaceae*) which contains **frangulin**.
- It is synonymous to Cascara sagrada.



45

- Anthraquinone laxatives should **not** be the first choice for treatment of constipation. **Bulk laxatives** are preferable.
- **Bulk laxatives:** increase the bulk in stool, an effect that helps cause movement of the intestines. It also works by increasing the amount of water in the stool, making the stool softer and easier to pass.
- The **smallest** dose that gives a satisfactory effect should be chosen.

❖ **CONTRAINDICATIONS:**

1. Intestinal occlusion.
2. Acutely inflammatory intestinal disease.
3. Appendicitis.

24

Laxatives

Laxative Type	Generic Name	Brand Name(s)
Bulk-forming	Methylcellulose	Citrucel®
	Polycarbophil	FiberCon®, Fiber-Lax®
	Psyllium	Metamucil®, Konsyl®
Lubricating	Glycerin	Glycerin suppository (generic)
	Mineral oil	Mineral oil (generic)
	Magnesium hydroxide (milk of magnesia) and mineral oil	Phillips® M-O
Stool Softeners	Docusate sodium	Colace®, Dulcolax® Stool Softener, Phillips' Liqui-Gels®
Saline	Magnesium hydroxide (milk of magnesia)	Ex-Lax® Milk of Magnesia Laxative/Antacid Phillips® Chewable Tablets Phillips® Milk of Magnesia
Stimulant	Bisacodyl	Ex-Lax Ultra, Dulcolax Bowel Prep Kit
	Sodium bicarbonate and potassium bitartrate	Ceo-Two Evacuant®
	Sennosides	Ex-Lax® Laxative Pills
	Castor oil	Purge®
	Senna	Senokot®
Osmotic	Polyethylene glycol 3350	GlycoLax®, MiraLAX®
	Lactulose	Kristalose®

Laxative Selections Guidelines

- The initial choice is usually a bulk-forming laxative
- Acute constipation is the primary indication for OTC laxatives. They are also used for preparing for diagnostic GI procedures
- Laxative use is supervised by a physician in patients in whom straining should be avoided (after surgery or MI) or in chronic constipation
- Laxative use is inappropriate in case of intestinal pathology

Laxatives: Mechanism of Action (cont'd)

Bulk forming

- High fiber
- Absorbs water to increase bulk
- Distends bowel to initiate reflex bowel activity
- Examples: Dietary fibre: bran (It absorbs water in the intestine ,swells,increases water content of faeces-softens it and facilitates colonic transit)
 - psyllium (**Metamucil**)
 - methylcellulose (**Citracel**)
 - polycarbophil

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27

• Side effects of anthraquinone cathartics:

1. **Gastrointestinal compliance.** 10 gm can lead to loss of electro^l specially K⁺ (**Hypokalemia**) which may cause inhibition of intestinal motility.
2. Long term uses can cause **albuminuria** and **hematuria**.
3. In rare cases, anthraquinones cause **heart arrhythmia, nephropathy, edemas, accelerated bone deterioration**.

• Interaction:

- ❖ Loss of K⁺ ion on long term **CAN ENHANCE THE EFFECT OF CARDIAC GLYCOSIDES, increasing their toxicity.**
- ❖ Anthraquinone glycosides should not be given to **pregnant** women and **children**.

28

Carmine

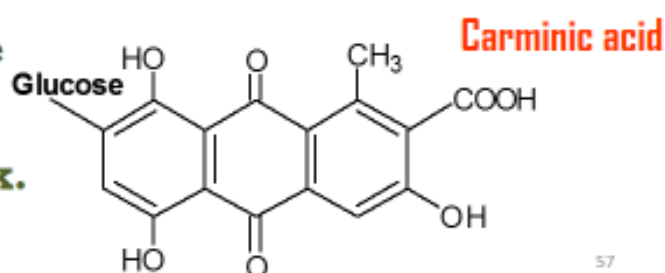
- ❖ A red pigment obtained from the **cochineal louse** القملة القرمزية, *Dactylopius coccus* which lives on cactae (singular: cactus صبار) of the genera *Opuntia* and *Napalea* (*Cactaceae*) in Mexico and Peru.
- ❖ It has been brought to the West Indies, the Canary Island and Spain.
- ❖ The **dried female** insect – the crude drug **cochineal** – contains about 10 % of the intensely, red water-soluble colouring matter, **carminic acid**, a C-glycoside of an AQ derivative.

29

Carmine

- ❖ **Carminic acid**: is a concentrate containing about 50 % carminic acid {**E-120**}.
- ❖ **Uses**: cochineal and carmine have been used as **colouring** matter for **lipstick**, **food**, **confectionaries** and **beverages**. They are believed to be less harmful than the synthetic pigments.

❖ **Can cause severe allergies and anaphylactic shock.**





31

Hypericin:

- Is a red-coloured, dimeric AQ derivative which is present in the **leaves** and **flowers** of *Hypericum perforatum* (St. John wort). العرن المثقوب, نبتة القديس جون.

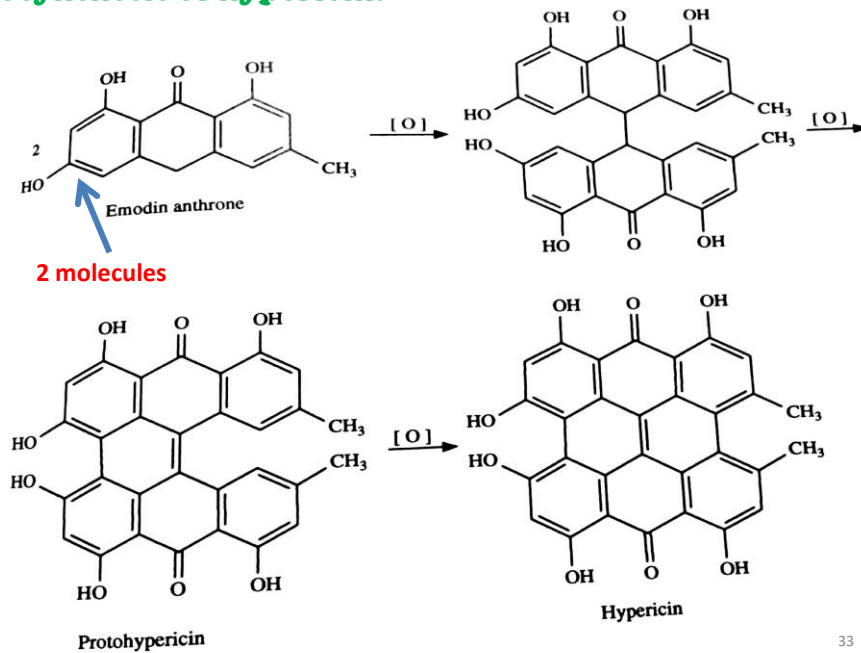


Biosynthesis:

- Hypericin is formed from **two** molecules of **emodin** anthrone by **oxidative phenolic coupling** (see figure).

32

Biosynthesis of hypericin:

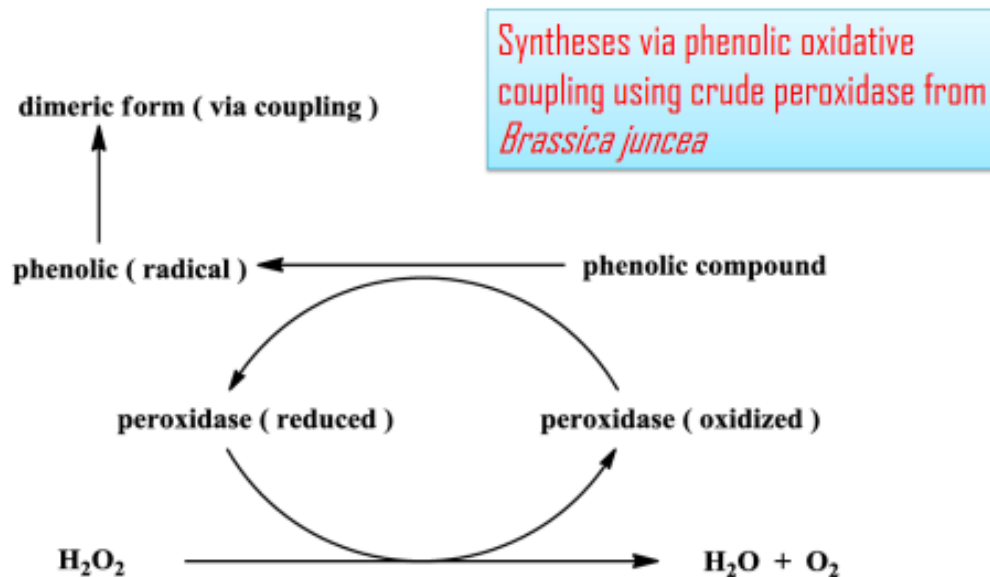


33

- Oxidative phenolic coupling is a widespread phenomenon both in the plant and animal kingdoms
- Several enzymes catalyze this reaction. They have an **iron** or **copper** as a *prosthetic group* (**The prosthetic group may be organic (such as a vitamin, sugar, or lipid) or inorganic (such as a metal ion), but is not composed of amino . Prosthetic groups are bound tightly to proteins and may even be attached through a covalent bond, as opposed to coenzymes, which are loosely bound**).
- All are able to affect one-electron transfer.
- Hydrogen peroxide and molecular oxygen (H_2O_2 and O_2), used as *oxidants*, are ultimately reduced to water.
- The transition metal catalysts shift between their oxidized and reduced forms.
- For the *phenol* part, the enzyme removes one electron and the phenoxy *radical* formed can couple in a number of ways.

34

Oxidative phenolic coupling



67

- **Hypericin** is a *photosensitizing* agent and causes the so called “**light sickness**” in animals feeding on *Hypericum*.
- Animals with white or light-colored coats display the symptoms upon exposure to light following feeding.
- **Symptoms:**
 1. *Psychomotor excitement* (**a series of unintentional and purposeless motions that stem from mental tension and anxiety**).
 2. *Efflorescence* (**redness of skin**) in form of blisters like those caused by burns.
 3. In serious cases, the poisoning results in:
 - a. Hemolysis.
 - b. Epileptic fits, and
 - c. Death of animals.

69

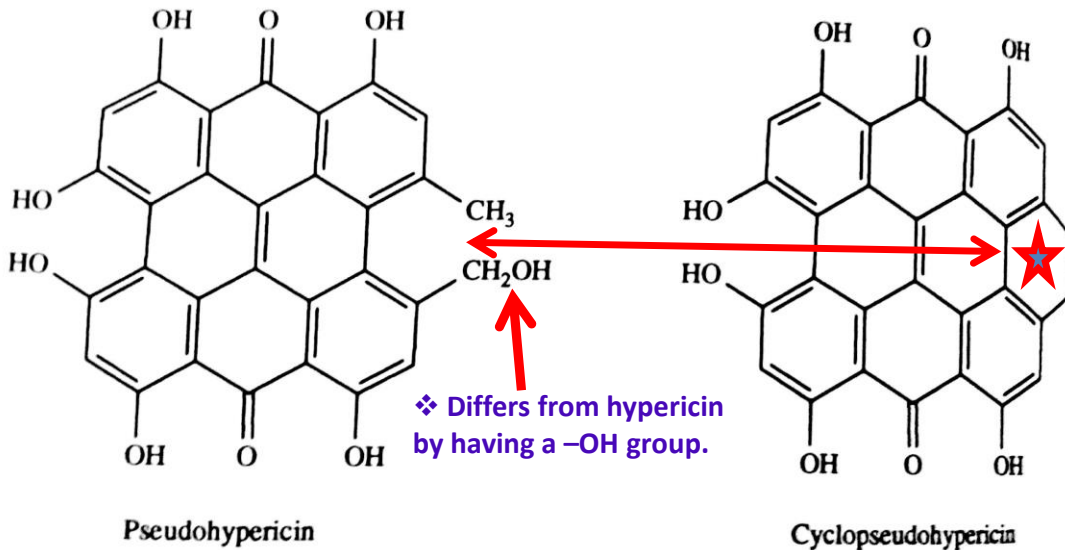
- Hypericin has **antiviral activity** against *retoviruses* such as **influenza** virus and **Herpes simplex** virus both *in vitro* and *in vivo* presumably **by acting directly on the virus particularly on the membrane components**.
- It has no activity on the transcription, translation or transport of viral proteins to the cell membrane and it has also no direct effect on the polymerase (**an enzyme that synthesizes long chains or polymers of nucleic acids**).
- Hypericin has been thought to be responsible for the **antidepressant activity** of extracts of Hypericum.

Hypericum:

- Is the dried flowers and aerial parts of St. John Wort, *Hypericum perforatum* العرن المثقوب أو نبتة سانت جونز أو نبتة سيدي يحيى (*Clusiaceae*).
- Is a herbaceous perennial plant which is widely distributed in Europe, Asia and Northern Africa, and now also naturalized in the USA.

36

- Hypericin is the main component among the group of dimeric AQ derivatives present in the plant. Other components are: **protohypericin**, **pseudohypericin** and **cyclopseudohypericin**.



1. Hypericum is a well-known herbal remedy as an **anti-inflammatory** and **wound-healing** agent.
2. Also, the *ethanol-water extracts* of the crude drug are known for their **antidepressant activities** (daily doses: 200-900 mg).

The antidepressant activity:

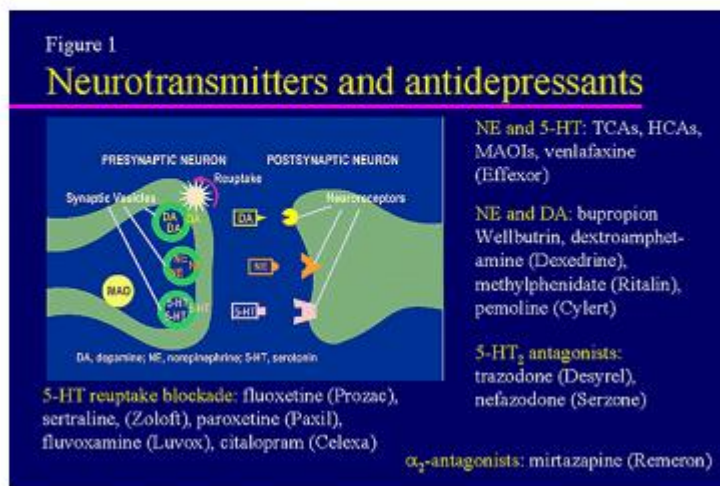
- ❖ The extract **inhibits** the synaptosomal uptake of norepinephrine, serotonin and dopamine.
- ❖ **Induces β -receptor down-regulation** and **up-regulation** of serotonin **5-HT₂** receptors when given subchronically to rats, and is **active** in a large variety of behavioural models indicative of antidepressant activity.
- ❖ However, MAO-A and MAO-B inhibiting properties of the extract are probably **too weak** to contribute significantly to its antidepressant activity i.e. **Antidepressant activity is probably not due to these inhibitory properties.**

Note:

- Serotonin, melatonin, noradrenaline, and adrenaline are mainly **broken** down by MAO-A.
- Phenethylamine and benzylamine are mainly **broken** down by MAO-B.

75

Antidepressant effect by inhibition of the reuptake of neurotransmitters



77

- ❖ **Hypericin** *might* be involved in the antidepressant activity. Most commercial extracts today are standardized on the content of hypericin.

Interactions of Hypericum:

- It can *interact* with many prescribed medicines such as **warfarin**, **cyclosporin**, **theophylline**, **digoxin**, **HIV protease inhibitors**, **HIV non-nucleoside reverse transcriptase inhibitors**, **anticonvulsants** (antiepileptics), **selective serotonin reuptake inhibitors** and **oral contraceptives**.
- **The reason of this interaction** is that hypericum (particularly, hyperforin) **activates pregnane X receptor (PXR)**, the receptor that regulates expression of **cytochrome P450-3A4 (CYP3A4) monooxygenase**. Activation of PXR induces expression of CYP3A4 which is **involved in the oxidative metabolism** of more than **50 % of all drugs**, which means **more rapid** metabolism and hence **lower** plasma levels of the prescribed medications.

39

- ❖ Accordingly, dose adjustment is necessary especially with drugs such as **warfarin** and **cyclosporin** (immunosuppressant drug widely used in organ transplantation to prevent rejection).

- ❖ In addition, stopping of hypericum intake while taking such drugs can result in serious problems due to the elevated plasma levels of these medications.

- ❖ It is noteworthy that hypericin **does not** have any effect on any enzyme member in the cytochrome p-450 family.

40